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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	3460-P04668US01	1864

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,24,28,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,24,28,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Finality of the previous office action of July 23, 2010 has been withdrawn and the prosecution on the merit has been reopened in view of new rejections.

This action is non-Final.

Applicant's amendments and response filed October 25, 2010 has been received and entered. Claims 3-23, 25-27, 29-42 have been canceled, while claim 1, 44 have been amended. Claims 1-2, 24, 28, 43 and 44 are pending and under consideration in the instant application.

Withdrawn-Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 28, 43 and 44 were rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants' amendments to the claims and arguments filed October 25, 2010 have been fully considered and found persuasive; therefore, previous rejection to the claims 1-2, 28, 43 and 44 set forth on pp. 2-4 of the previous office action dated July 23 is hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-2, 28, 43 and 44 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' cancellation of claim 24 renders their rejections moot. Applicants' amendments to the base claim deleting the recitation of large gene deletion obviates the basis of the rejection of claims 1-2, 28, 43 and 44.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 24, 28, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al (US Patent no 6,251,957, dated 6/26/2001, art of record), Conti-Fine (US 6,929,796, dated 8/16/2005, filed on 12/16/1997, art of record) and Nilsson et al (Proc. Natl. Acad. Sol. USA: 1986, 83, 9169-9173).

Claims are directed to a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral vector, said mammal showing symptoms of hemophilia B and having a genetic defect has which can result in generation of inhibitory antibodies to Factor IX upon administration of exogenous Factor IX, said method comprising intravenously or intraperitoneally administering to said mammal cyclophosphamide prior to or simultaneously with said adeno-associated viral vector delivery before formation of said inhibitory antibodies, the delivered Factor IX being from the same species as said mammal. Subsequent claims limit base claim, wherein said mammal and gene are human. Claim 28 limit the method of claim 1, wherein said cyclophosphamide is administered concomitantly with said adeno-associated viral vector. Claims 43, 44 limit the method of claims 1, wherein Factor IX production in said mammal induces formation of said inhibitory antibodies which are optionally determined by Bethesda titers and wherein said mammal vector is administered intramuscularly.

Claim interpretation: The method as claimed is interpreted comprising intravenously or intraperitoneally administering to a mammal cyclophosphamide.

Wilson teaches a gene therapy method of inhibiting in a mammal formation of neutralizing antibodies directed against a virus comprising the step of co-administering to said mammal said virus and a combination of immune modulators which inhibits neutralizing antibodies against said virus, wherein the combination of immune modulators consists of

cyclophosphamide and an anti-CD4 monoclonal antibody (col. 25-26). Wilson teaches a gene therapy method comprising co-administering with a viral vector comprising a heterologous nucleotide sequence and an immunosuppressive agent to a human (col. 2, lines 35-52, column 4, lines 20-34 and col. 25-26). Wilson teaches that the viral vector can be AAV (col. 26). Wilson teaches that an immune response can be the product of the transgene when that transgene expresses a protein that is foreign to the treated host (col. 1). Wilson teaches that the immunosuppressive agent may be administered prior to or concurrently with the recombinant viral vector (col. 2, lines 45-49). It is further included that immune modulator is administered by the same route as the recombinant vector that includes intravenous, IM injections (col. 10, lines 40-41, col. 9, line 55). However, Wilson does not specifically using the method to inhibit or prevent inhibitory antibodies against the protein being provided via gene therapy, wherein the protein is encoded by a heterologous nucleotide sequence that is from the same species as said mammal.

However, at the time the invention was made, hemophilia mammals that do not produce factor VIII or Factor IX, but produce anti-factor VIII or anti-factor IX antibodies after exogenous administration of factor VIII or IX were well known to one of ordinary skill in the art as exemplified by Conti-Fine (col. 3-6 and 15). Conti-Fine further teaches one of ordinary skill in the art would want to use an immunosuppressive agent in combination with gene therapy to inhibit antibodies against the protein(s) because the protein or viral proteins are foreign to the subject and the subject would develop an immune response to these proteins (col. 6-7). Conti-Fine teaches a method of inhibiting or preventing inhibitory antibodies to Factor IX in a subject (e.g., humans) comprising administering an immunosuppressive agent, wherein the Factor IX is delivered via gene therapy to the subject (abstract and col. 3-7, 14-15, and 30). The gene therapy to the subject (e.g., human) comprising administering viral vector comprising Factor IX being from the same species as the subject (col. 4-6 and 14, lines 31-57, and col. 15). The viral vector can be an adeno associated viral vector (col. 6, 15, and 27, line 61). Conti-Fine et al do not teach a method comprising administering cyclophosphamide to inhibit formation of inhibitory antibody against Factor IX.

However, at the time the invention was made, Nilsson teaches a complication of Factor IX therapy is the development of antibodies to Factor IX (page 9169). In this regard, Nilsson et

al teach a method of treating formation of inhibitory antibody to Factor IX, said method comprising administering high doses of intravenous injection of cyclophosphamide in combination with intravenous IgG and factor IX to a subject having severe hemophilia B and hlgh-responding antibodies (see abstract). Nilsson further teaches determining the formation of inhibitory antibody in plasma optionally by BIU (see page 9170, col. 1, para. 3).

At the time of filing of this application it would have been obvious to one of ordinary skill in the art to combine the teaching of Wilson taken with Conti-Fine and Nilsson to use a gene encoding Factor IX of same species as the species being treated in the method comprising intravenous injection of cyclophosphamide in combination with other immunosuppressant such as IVIgG , to prevent of inhibitory antibody to factor IX, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. Said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in art would be motivated to combine the teaching because prior art disclosed that deficiency in factor IX causes hemophilia B and replacement therapy to treat the genetic defects which result in disease is to introduce a "normal" gene that encodes the endogenous protein to the mammal having the deficiency result in an immune response to the foreign proteins, the endogenous protein, the recombinant polypeptide, or the viral capsid or glycoprotein and therefore would requires use of an immunosuppressive agent in combination with gene therapy (supra, see col. 14, lines 31-55). It would have been obvious to one of ordinary skill in the art to make such a modification, as it was an art recognized goal to inhibit the inhibitory antibody using immunosuppressant as disclosed by Wilson and Nilsson et al. One of skill in the art would have had a reasonable expectation of success in combining the teachings of Wilson with those of Conti-Fine and Nilsson because prior art recognized that administration of exogenous Factor IX (gene or protein therapy) in a subject having genetic defect and hemophilia B results in formation of inhibitory antibody that would require use of immunosuppressant, while Nilsson et al describe successful prevention formation of inhibitory antibody to Factor IX.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to arguments

To the extent that Applicants' previous arguments filed on 10/26/2006 and 6/11/2007 are pertinent to the new rejection, they are addressed as follows:

Applicant argue that the scientific literature is replete with studies in which immune-suppressive agents either failed completely, caused unacceptable adverse side effects, or was limited in duration and effectiveness. Applicants cite various section of Wilson *et al.* patent who reported that using CD4 antibodies and CD40L antibodies for immunosuppression did not prevent neutralizing antibodies from forming (column 18, lines 52-56; column 22, Table III; and column 23, lines 22-28). Applicants further cite Nilsson et al. (Proc. Natl. Acad. Sci. USA 83:9169 (1986)), to assert that the "treatment with factor IX and cyclophosphamide was ineffective, resulting in high and persistent anamnestic response." (see page 9173, first sentence under "Discussion"). Thus, in view of the foregoing, it is clear that the art indicates that immunosuppressive agents frequently fail to reduce or prevent formation of inhibitory antibodies in a wide variety of contexts. Consequently, in view of the art, the skilled artisan would not have had a reasonable expectation of success at the time of the invention. Applicants' arguments have been fully considered, but are not found persuasive.

As an initial matter, base claim 1 is broad and requires only one active method step comprising intravenously or intraperitoneally administering to a mammal cyclophosphamide prior to or simultaneously with the adeno-associated viral vector delivery. The claimed method as recited is not limited to cyclophosphamide administration, rather read on administration of other immunosuppressant.

Applicants have further engaged in selective reading of the teachings of Wilson et al. and Nilsson et al to formulate the grounds for teaching away. It should be noted that Wilson et al teach a gene therapy method of inhibiting in a mammal formation of neutralizing antibodies directed against a virus comprising the step of co-administering to say mammal said virus and a combination of immune modulators which inhibits neutralizing antibodies against said virus, wherein the combination of immune modulators comprises cyclophosphamide (col. 25-26). Nilsson et al teach a method of treating formation of inhibitory antibody to Factor IX, said method comprising administering high doses of intravenous injection of cyclophosphamide in combination with intravenous IgG and factor IX to a subject having severe hemophilia B and

high-responding antibodies (supra). Applicant should note that claimed method is not limited to administration of single immunosuppressant. Therefore, to the extent Nilsson et al describe successful prevention of inhibitory antibody to factor IX upon exogenous administration of Factor IX in a method comprising administering high doses of intravenous injection of cyclophosphamide and other agents, the rejection is applicable to the case. Thus, contrary to applicants' assertion, prior art recognized method comprising administration of cyclophosphamide resulted in inhibition of inhibitory antibody to exogenous administration of Factor IX. To the extent, Wilson teaches a gene therapy method of inhibiting in a mammal formation of neutralizing antibodies directed against a virus comprising the step of co-administering to said mammal said virus and a combination of immune modulators which inhibits neutralizing antibodies against said virus vector, wherein the combination of immune modulators comprises cyclophosphamide and an (col. 25-26), the rejection is applicable to the instant case. Applicants' selective reading of Wilson et al. ignores the teachings of the reference of Nilsson. There is no requirement for Wilson et al. to teach that which is clearly taught by Nilsson et al. A person of skill in the art would be motivated to use a gene encoding Factor IX of same species as the species being treated in the method comprising intravenous injection of cyclophosphamide in combination with other immunosuppressant such as IVIG , to prevent of inhibitory antibody to factor IX.

Applicant argues that there must have been a motivation to produce the claimed methods at the time of the invention, and that the prior art must be considered in its entirety, including portions that teach away. In this regard, the art is replete with studies indicating the absence of inhibitory antibody formation against proteins delivered by way of gene therapy. Applicants provide the reference of Tripathy et al. (Nat. Med. 2:545 (1996)) to state that mice injected with adenovirus harboring human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring murine EPO did not develop anti-EPO antibodies. Herzog (Blood 90, part 1, Supp. 1, abstract 1057 (1997))) reported that antibodies against Factor IX following injection with an AAV vector with canine Factor IX into a hemophiliac dog (hemophilia B) were not detected (see page 5 of the argument filed 6/11/2007 and page 8 of arguments filed 10/26/2006). Applicants have previously submitted exhibits A to D corroborate that human or canine subjects with hemophilia A or B, including subjects incapable of producing endogenous Factor IX did not

produce detectable inhibitors against Factor IX (Manno *et al.*. Blood 101:2961 (2003), and Mount *et al.* Blood 99:2670 (2002)). Thus, in view of the absence of inhibitor antibodies the skilled artisan would not have been motivated to administer cyclophosphamide (see page 6 of the arguments).

Such is not found persuasive because cite prior art summarized by the reference of Nilsson clearly teaches a complication of Factor IX therapy is the development of antibodies to Factor IX (page 9169). Additionally, Conti-Fine also teaches that hemophilia mammals that do not produce factor VIII or Factor IX, but produce anti-factor VIII or anti-factor IX antibodies after exogenous administration of factor VIII or IX as exemplified by Conti-Fine (col. 3-6 and 15). Specifically, Conti-Fine disclose that deficiency in factor IX causes hemophilia B and replacement therapy to treat the genetic defects which result in disease is to introduce a "normal" gene that encodes the endogenous protein to the mammal having the deficiency result in an immune response to the foreign proteins, the endogenous protein, the recombinant polypeptide, or the viral capsid or glycoprotein and therefore would requires use of an immunosuppressive agent in combination with gene therapy (see col. 14, lines 30-55 and col. 15).

It is relevant to point out that applicant choose not to address the teaching of Conti-Fine that specifically provide guidance of formation of inhibitory antibody, instead provided other art summarized by the references of Tripathy et al. (Nat. Med. 2:545 (1996)), Herzog (Blood 90, part 1, Supp. 1, abstract 1057 1997), Manno *et al.*. Blood 101:2961 (2003), and Mount *et al.* Blood 99:2670 (2002) that do not teach formation of inhibitory antibody. It should be noted that claims require a subject having genetic defect that shows symptoms of hemophilia B. In this regard, applicant should note that Tripathy et al and Herzog do not teach any such subject having genetic defect showing symptoms of Hemophilia B, therefore, these references are not pertinent to the instant claims. Manno and Mount *et al.* Blood 99:2670 are post filing art that involves additional method steps that are not present in the pending claims. Further, examiner has provided new reference that shows presence of inhibitory antibody in subject having hemophilia B (see Nilsson et al). Additionally, Conti-Fine also teaches inhibiting or preventing inhibitory antibodies to Factor IX in a subject (e.g., humans) comprising administering an immunosuppressive agent, wherein the Factor IX is delivered via gene therapy to the subject (abstract and col. 3-7, 14-15, and 30). In view of foregoing, it is clear that one of ordinary skill in

the art would be motivated to combine the teaching to administer an immunosuppressive agent, wherein the Factor IX is delivered via gene therapy to the subject in view of the teaching in prior art, as required by the claims.

Applicants have previously submitted evidence of unexpected results, wherein Exhibit A was provided with a data summary of 10 dogs treated in accordance with the claimed methods which were followed up to 3.5 years. As discussed, none of the 10 dogs produced detectable inhibitory antibodies against Factor IX up to 39 months after receiving cyclophosphamide with gene therapy (see page 6 of the arguments).

Such is not found persuasive because previously provided exhibit A compare 10 dogs treated in accordance with the claimed method to 2 untreated dogs without showing any statistical significance of the results. It should be noted that any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, claims requires only one active method step that is clearly taught by combination of references (supra). Nilsson et al teach a method of treating formation of inhibitory antibody to Factor IX, said method comprising administering high doses of intravenous injection of cyclophosphamide in combination with intravenous IgG and factor IX to a subject having severe hemophilia B and high-responding antibodies (see abstract). Therefore, the fact that method comprising administering high doses of intravenous injection of cyclophosphamide to inhibit inhibitory antibody to exogenously administered FIX is an expected result, and is the goal behind administering immunosuppressant to exert greater beneficial effect as compared to subject without treatment of immuno suppression. As indicated in MPEP 716.02(c), Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). An affidavit or declaration under 37 CFR 1.132 must

compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979).

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Smith et al (Gene Therapy (1996), 3(6), 496-502) and Dwarki et al (WO9906562).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632